

Review

Childhood leukaemia risks: from unexplained findings near nuclear installations to recommendations for future research

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Abstract

Recent findings related to childhood leukaemia incidence near nuclear installations have raised questions which can be answered neither by current knowledge on radiation risk nor by other established risk factors. In 2012, a workshop was organised on this topic with two objectives: (a) review of results and discussion of methodological limitations of studies near nuclear installations; (b) identification of directions for future research into the causes and pathogenesis of childhood leukaemia. The workshop gathered 42 participants from different disciplines, extending widely outside of the radiation protection field. Regarding the proximity of nuclear installations, the need for continuous surveillance of childhood leukaemia incidence was highlighted, including a better characterisation of the local population. The creation of collaborative working groups was recommended for consistency in methodologies and the possibility of combining data for future analyses. Regarding the causes of childhood leukaemia, major fields of research were discussed (environmental risk factors, genetics, infections, immunity, stem cells, experimental research). The need for multidisciplinary collaboration in developing research activities was underlined, including the prevalence of potential predisposition markers and investigating further the infectious aetiology hypothesis. Animal studies and genetic/epigenetic approaches appear of great interest. Routes for future research were pointed out.

Keywords: childhood, leukaemia, risk, nuclear installations, aetiology, epidemiology

1. Introduction

Leukaemia is the commonest type of childhood malignancy, accounting for ~30% of all diagnoses in children less than 15 years of age in economically developed regions of the world. The heterogeneous nature of leukaemia is well established. In childhood, the major subtypes are acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) with ALL occurring approximately five times more frequently than AML [1, 2]; chronic myeloid leukaemia (CML) also occurs rarely. Acute leukaemia can be further classified into distinct subtypes according to cell lineage, stage of immunophenotypic maturation and specific molecular genetic abnormalities [3]. Of these, B-cell-precursor ALL is the commonest subtype. In contrast to other subtypes like T-cell ALL or AML, its incidence has a distinct age peak in children aged two to five years [4].

Many factors have been proposed to be causative of childhood leukaemia [5–7]. However, to date, the only established risk factors for childhood leukaemia are Down syndrome, sex (with boys more often affected than girls, with a ratio ~1.2 : 1), chemotherapeutic drugs and acute exposure to ionising radiation at moderate and high doses (above 100 mSv). Several studies suggested that risk may exist at lower radiation doses and dose rates, and that this risk is compatible with current predictions [8–11]. In 1990, the hypothesis of hereditary radiation effects on childhood leukaemia risk was proposed by Gardner *et al* to explain the Sellafield cluster [12], but consecutive negative studies lead to the rejection of this hypothesis [13, 14]. Exposure to 50 Hz electric and magnetic fields (ELF-EMF) is also suggested as a risk factor for childhood leukaemia [15], but there is as yet no biological evidence supporting the epidemiological evidence [16]. There is consistent evidence from

epidemiological studies that high birth weight is a determinant of disease risk [17–19]. The role of exposure to infectious agents and immune function in relation to risk of childhood ALL is also under investigation [20, 21], but the mechanisms by which these factors could play a role are still not clear.

Living near a nuclear facility became a suspected risk factor for childhood leukaemia after the 1984 report on an increased leukaemia risk in the village of Seascale close to the British nuclear fuel reprocessing plant of Sellafield [22]. Since then, a number of studies have investigated the leukaemia risk near nuclear facilities, including nuclear power plants (NPPs), and several reviews were published [23–25]. Between 2008 and 2011, several meetings were held and several committees were convened to review existing results of cancer risks around nuclear facilities and provide recommendations, e.g. in Germany [7, 26], in France [27], in Sweden [28] and in the UK [29]. Based on the recommendations from these meetings, the German Federal Office for Radiation Protection (BfS) and the French Institute for Radiological Protection and Nuclear Safety (IRSN) decided to organise a focused workshop on the topic of future research on childhood leukaemia, bringing together researchers from a wide range of related disciplines. This workshop was organised under the auspices of the Multidisciplinary European Low Dose Initiative (MELODI, www.melodi-online.eu) and was held in France in June 2012. The Workshop had two aims: (a) to review the latest results and to discuss methodological limitations of studies of childhood leukaemia incidence close to nuclear installations; and (b) to identify new directions for future research into the causes and pathogenesis of leukaemia in children. Thus, the Workshop did not just cover the effect of radiation-related leukaemia risk, but also other major known or suspected risk factors of childhood leukaemia.

This paper summarises the results of the Workshop. Its first part deals with the issue of childhood leukaemia risk near nuclear installations and focuses on a review of available findings, the design of epidemiological studies and suggested improvements for the future. The second part concerns the aetiology of childhood leukaemia and the underlying disease biology (B-cell development and haematopoietic stem cells (HSCs)), environmental, infectious and genetic risk factors and the relevance of animal models. Recommendations are then detailed.

2. Studies of childhood leukaemia risk near nuclear installations

A major aspect of the Workshop was to discuss the current hypothesis regarding an excess risk of childhood leukaemia near nuclear installations. Participants provided an overview of studies undertaken in Europe in recent years and of those planned in the United States. Special attention was paid to leukaemia risk in the youngest age group. Due to the diversity of epidemiological designs and analysis methods, methodological aspects of recent studies were considered.

2.1. Review of current knowledge about the risk of childhood leukaemia near nuclear installations

Based on a combination of several criteria (statistical significance, validity of the methodology, confirmation by different authors using different approaches and persistence over time), the Workshop participants agreed that there is convincing evidence for three confirmed clusters of childhood leukaemia near nuclear installations: these are near the Sellafield reprocessing plant in Cumbria, England; the Dounreay reprocessing plant in Northern Scotland; and the Kruemmel NPP in Northern Germany [23]. However, leukaemia clusters also have been

reported elsewhere and are not specific to nuclear installations. For example, the Fallon cluster in Churchill County, Nevada, is a striking example of a leukaemia cluster [30]: 14 children were diagnosed with ALL during the period 1997–2003 while only three to four cases were expected. Despite the comprehensive public health investigation launched by the US Centers for Disease Control and Prevention (CDC) the cause of the cluster remains unknown.

Several reviews of childhood leukaemia risks near nuclear installations already exist [23–25, 31, 32], as well as a meta-analysis [33], which has been criticised due to doubts over the validity of the selection process and potential publication bias [29, 34, 35]. The review of results from multisite studies was updated during the Workshop by considering studies about childhood leukaemia risk near NPPs published after 2008 (Germany [36, 37], Switzerland [38], France [39, 40], Finland [41], Great Britain [29] and Belgium [42]). Consistent with other authors [43], the Workshop participants noted that, even when the associations are not statistically significant, the results from these recent studies demonstrated some elevated risk of childhood leukaemia when considering the 0–4-year age category within 5 km from a NPP. However, results are based on small numbers, and considerable methodological differences between studies (design, statistical analyses, periods covered, diagnosis quality and administrative units analysed) do not allow the combination of their results by simply adding numbers. Moreover, a compilation of results available for the complementary 5–14 year age category performed during the Workshop did not indicate an elevated risk of childhood leukaemia in this age category.

Based on the available literature, the Workshop participants concluded that there was no elevated risk of childhood leukaemia globally near NPPs in children less than 15 years old.

The rather consistent pattern of increased leukaemia risk in the 0–4-year olds needs to be verified in the future and should not be interpreted as a causal association, but it may provide clues about a possible link between childhood leukaemia and living in the close proximity of a nuclear facility (see [44]).

Two new studies have been published since the Workshop. The first one considered cancer incidence within 25 km of the three Ontario NPPs using an ecological study design [45]. The second is a case–control study including all leukaemia and non-Hodgkin lymphoma cases diagnosed below age five years in Great Britain, and analysing risk related to distance from 13 NPPs [46]. Both studies showed no excess risks near NPPs. Nevertheless, as in previous studies, the numbers of cases were small when focusing on the 0–4 year age category within 5 km of the NPPs. The US National Research Council (NRC) recently published a report on the assessment of cancer risks in populations near US nuclear facilities [47]. The NRC committee recommended considering two different study designs: (1) an ecologic study of multiple cancer types of populations living near nuclear facilities and (2) a record-linkage-based case–control study of cancers in children born near nuclear facilities. Testing the feasibility of a dose assessment was also recommended. The launch of a pilot study, based on seven nuclear installations located in six US states, was announced in October 2012.

2.2. Methodological aspects of studies performed

2.2.1. Epidemiological design. Most of the studies performed since the early 1980s have been of ecological design (i.e. average rates in geographical areas). This type of analysis can be subject to well-known types of bias (ecological fallacy, migration, sensitivity to the arbitrary choice of the study perimeter, etc). Thus, more recent studies used individual based designs, i.e. case–control [36, 40] and cohort design [38, 41]. Whilst these approaches can avoid some of the limitations associated with ecologic study design, other limitations exist (selection bias,

participation bias, migration bias, lack of control of confounding factors, small sample size, etc). Furthermore, response bias specific to case-control studies is well documented [48, 49]. Indeed, at the German KiKK study data from a detailed questionnaire were not used due to the potential response bias [36]. Nevertheless, if the geographic unit used in an ecologic study is small enough (for example municipalities in France), results from case-control and ecologic studies are in agreement [36, 37, 40]. In conclusion, for the specific question of childhood leukaemia incidence near NPPs, no clear preference is evident; each design presents advantages and limitations. Future study protocols have to be developed according to the availability of data, the input required versus the scientific return and the hypotheses to be tested, with specific attention paid to minimise potential biases. Notwithstanding this, efforts to evaluate the feasibility of combining data from different existing studies to increase statistical power might be useful.

2.2.2. Power and prior hypothesis. The Workshop participants underlined the necessity for a continuing surveillance of childhood leukaemia incidence near NPPs, but not limited to NPPs. Nevertheless, they recommended that no new studies are set up before an explicit hypothesis is formulated. The main analysis to test this hypothesis must be specified, and the associated statistical power must be calculated *a priori* (which is not systematically done in the usual practice). Multisite studies are preferred to single-site studies, as they have a greater statistical power and provide a broader context for the interpretation of results, i.e. comparing risks between sites of similar characteristics.

Large-scale studies, not focused on potential sources of risk, are useful with respect to the question of whether childhood leukaemia has the tendency to cluster. Hitherto, results are not consistent (e.g. [50–53]). The issue of clustering is important for the interpretation of local clusters (in particular with respect to the infection hypothesis) and should be investigated further, but independently from the existence of nuclear sites. It was also concluded that new studies on childhood leukaemia near nuclear installations should aim to look at other potential causes of leukaemia.

2.2.3. Pertinent outcomes. The Workshop participants agreed that it was reasonable for studies near nuclear sites to have considered childhood leukaemia as the main potential outcome; but given the heterogeneity of the diseases collectively described as ‘leukaemia’, future studies should distinguish between leukaemia subtypes. Combined analyses of data from several countries in Europe may allow the accumulation of a sufficiently large number of cases for such subtype-specific analyses. Further, the unclear and somewhat arbitrary (at least, historically) distinction between some forms of childhood NHL and some forms of childhood ALL must be borne in mind.

Other outcomes may be considered, but only if they are clearly hypothesis-driven. For example, the Belgian NUCABEL study considered thyroid cancer in addition to childhood leukaemia, because the study was ordered following the Fleurus nuclear incident involving releases of iodine-131 [42]. Among pathologies that were hypothesised to be potentially associated to either pre-conceptional [54] or *in utero* exposure, congenital malformations might also be considered as a possible health indicator, as was done for example in Germany in parallel to the KiKK study [55]. It was noted that information on other diseases (especially childhood cancers other than leukaemia) might help with the interpretation of results in that, for example, a common bias could be manifest over all types of childhood cancer rather than just childhood leukaemia.

2.2.4. Exposure indicators. Distance can be easily and reliably determined, but it constitutes only a crude proxy for radiation exposure from nuclear installations. Better exposure indicators are needed for investigating health effects around nuclear sites. This recommendation is

in accordance with that of the NRC report which calls for absorbed doses to individual organs to be estimated [47].

Based on the results from exposure monitoring or dosimetric estimates, the orders of magnitude of the doses attributable to current routine discharges appear to be small. The so-called ‘radioecological studies’ conducted in the UK [56–58], in Germany [59] and in France [60, 61] indicated that the levels of doses attributable to releases from the plants were well below those due to natural sources of radiation (100 to 1000 times, or more) and could not explain the observed number of cases [62, 63]. The feasibility and pertinence of measurements of radionuclides (tritium and carbon-14 and possibly other radionuclides) in environmental media or directly in children (e.g. urine analysis), or other dosimetric approaches to evaluate individual doses should be investigated, as the direct measurement of the body contents of radionuclides such as caesium-137 and plutonium-239/240 have provided valuable information in the past (e.g. [58, 64, 65]).

It is also important that the characteristics of the local population (demography, sociology, socio-economic status (SES), life habits, day-care attendance, etc) are determined in as much detail as possible. Also, attention should be given to suspected potential environmental risk factors for leukaemia, such as ELF-EMF, pesticides, air pollution, and proximity of a petrol station or industrial sites.

2.3. Routes of improvement

The Workshop participants concluded that systematic registration of childhood leukaemia cases is needed based on exhaustive and standardised recording systems, including population-based registries. Continuation and development of ongoing registration activities have to be supported; this might include additional information to be collected in order to capture early life exposures. Reconstructing the exposure history of the children (place of birth, residential history, antenatal exposures, etc) is desirable, wherever possible with reasonable effort. Also, efforts should be made for studies to include collection of biological samples to support research into the pathogenesis of childhood leukaemia.

The Workshop participants encourage collaboration between teams involved in this research topic to bring together investigators from different studies, and control for methodological differences, in order to better interpret and evaluate the coherence and differences of the results obtained in various countries. Participation in cross-border initiatives would also facilitate investigating possible health effects in the vicinity of the many nuclear sites that are located close to national borders, as is in the case of France and Belgium (Chooz NPP). Also, the consideration of several potential confounders that may lead to differences in findings among countries—e.g. SES, urban–rural status, population density—should be considered; but the strong overlapping of these factors should be kept in mind in the interpretation of the results. Finally, collaboration should provide the framework for an international combined analysis, which is the best approach to the derivation of pooled risk estimates. A working group at the European level should verify the feasibility and pertinence of such pooling effort, with a special attention to minimising biases.

3. Aetiology and mechanisms of childhood leukaemia initiation and development

The second part of the Workshop focused on the aetiology and mechanisms of childhood leukaemia initiation and development, taking into account different environmental exposures and genetic risk factors [5]. It is the aim of international consortia like the Childhood

Leukaemia International Consortium (CLIC) [66] and the International Childhood Cancer Cohort Consortium (I4C) [67], to pool data to further understand the causes of childhood leukaemia. Workshop participants provided an overview of current knowledge and identified possible steps forward. Specific attention was given to B-cell-precursor ALL, which is the commonest subtype of childhood leukaemia.

3.1. *The multistep development of childhood leukaemia*

Childhood leukaemia is a heterogeneous disease, and its development is a multistep process [7, 68]. Current results indicate that the first step occurs *in utero* converting a haematopoietic precursor or stem-cell to a preleukaemic clone [69, 70]. Specific chromosomal translocations, as a result of DNA double strand break or high hyperploidy, arising probably from a single-step mechanism [71] are the commonest cytogenetic abnormalities in B-cell-precursor ALL. For example, the translocation RUNX1-ETV6 occurs with a frequency of approximately 20% in ALL, and high hyperploidy is found in 25–30% of ALL cases. It has been shown that approximately one in 100 new-borns carry the RUNX1-ETV6 translocation, which is a rate significantly higher than the overall incidence rate of ALL in the population [72]. This would imply that preleukaemic clones are frequent, and normally extinguished (or at least kept at bay) by natural processes. However, such high frequency of RUNX1-ETV6 translocation was not confirmed in another recent study [73].

Beyond the known genetic or epigenetic event(s), other elements must interact to lead to the development of acute leukaemia [74, 75], but so far, epidemiological studies have not been able to distinguish between the correlation of various potential risk factors with the initial and subsequent genetic events.

Efforts need to concentrate on determining the time of origin of the preleukaemic clone and its prevalence at birth, as this is important for the understanding of the role and pertinent time window at which risk factors under consideration would be involved [76]. The nature of the cell-of-origin cannot be identified by studying ALL samples at the time of diagnosis [77]. Thus, prospective designs have to be considered, and birth cohorts may prove of great interest. Given the rarity of the disease, a worldwide coordinated approach is needed to allow comparison of the prevalence of the preleukaemic clone in different countries and ethnic groups. So far, little is known about ALL incidence and trends in developing countries, but the incidence of pre-B ALL generally appears to be low in low-income and middle-income countries and increases substantially as countries undergo socio-economic development [78, 79].

3.2. *Inherited susceptibilities*

Childhood ALL arises as a consequence of a limited number of genetic alterations [80]. Several independent genome-wide association studies (GWAS) have confirmed a number of genetic variants that affect genetic susceptibility to ALL, although they are individually modest in their effects. In the most recent GWAS on ETV6-RUNX1-positive ALL, a few (ETV6-RUNX1-specific) susceptibility loci, predominantly related to pathways controlling embryonic and B-cell development and differentiation, were identified [81]. Based on copy number alterations, cases could be categorised into four distinct subgroups revealing genetic diversity within ETV6-RUNX1-positive ALL which is of importance for improving treatment strategies [82, 83]. Polymorphisms in many other pathways have been investigated in relation to risk of ALL such as DNA repair and cell cycle control genes [84, 85]. A meta-analysis on candidate genetic variations, however, saw significant associations in only eight out of 25 polymorphic variants [86]. GWAS revealed that common genetic variations contribute to the risk

of B-cell-precursor ALL [87]. On the other hand, a high concordance of subtypes of ALL within families has also been reported [88], indicating strong genetic and/or environmental risk factors are restricted to specific ALL subtypes. This implies that future studies on risk factors should distinguish between ALL subtypes. Similarly, leukaemias in infants and in young children are different genetic and clinical entities that should be examined separately in future epidemiological study.

Next-generation sequencing (whole genome or transcriptome sequences, exome capture and sequencing, analyses of the methylome) of ALL cases might uncover a common signature. In contrast to GWAS, deep sequencing focuses on mutations and other detailed differences e.g. in the epigenome, which could, at least partly, reflect the effects of the environment. As for other cancers [89, 90], this could help to characterise leukaemia subgroups that might not show up in an overall approach, or detect common patterns/footprints possibly correlated to external risk factors [91–93].

3.3. Developmental aspects

Haematopoiesis in the embryo occurs in stages [94]. The first stage occurs early in intra-uterine life and aims at producing red blood cells, whilst the second generates all lineages of blood cells and HSCs. During foetal life, HSCs are characterised by a high level of cell cycle activity (approximately 100% per 24h) and become quiescent upon seeding the bone marrow, a process finalised in humans at an age of approximately two years. The properties and functionality of the developing haematopoietic system may prove important for the onset, but also for the outcome of the disease. Indeed, different age groups are associated with different leukaemia subtypes: MLL-related B-cell ALL is the main subtype in the age group 0–1, while B-cell-precursor childhood ALL peaks around 2–5 years.

Cell cycle activity of HSCs is carefully modulated by a complex network of cell-intrinsic and cell-extrinsic mechanisms [94] and the understanding of the age-dependent cell cycle regulation might, therefore, provide clues to the development of leukaemia subtypes. Epidemiologic studies should aim at distinguishing the leukaemia subtypes associated to different age categories. Animal models may give further insight into haematopoiesis in different age groups and on external influences on these processes.

3.4. Microenvironment

In view of the high cell division rate during foetal and infant haematopoiesis and the mutation potential of lymphoid cells, any genotoxic compound as well as the weakening of cell cycle checkpoint stringency and immunological surveillance can increase malignant transformation.

The stromal microenvironment is known to be important for HSCs' proliferation, activity or quiescence, respectively, and for B-lineage development and differentiation. Leukaemia-specific genetic aberrations have been found in the mesenchymal stem cells in some ALL cases [95]. Overall, the role of the microenvironment on the persistence of preleukaemic clones and the plasticity of leukaemia cells needs to be uncovered. In a mouse model the lineage fate of leukaemia cells (B-cell ALL versus AML) was determined by the host microenvironment [96].

3.5. Immune system and the infectious hypothesis

The hypothesis that childhood leukaemia is a rare response to an infection is persistent. Kinlen suggested that childhood leukaemia could arise as a rare consequence of exposure to a specific

unidentified common infection, the rare outcome being particularly evident at times of unusual population mixing, when a relatively large number of susceptible children encounter a relatively large number of infected individuals leading to (largely subclinical) epidemics [21, 97–99]. It has been suggested that the construction of a nuclear facility in a rural area might promote unusual social contacts and population mixing that could represent at least a cofactor of the risk observed [98]. This infection hypothesis could also provide an explanation for the leukaemia cluster in Fallon, USA [30, 100]. Greaves hypothesised that a paucity of exposure to infectious agents in the first year of life and subsequent ‘delayed’ infectious challenge may be causal in the development of B-cell-precursor ALL in the peak ages two to five years [20, 101]. This hypothesis is supported by studies that have looked at self-reported day-care attendance as proxy for social contacts [102], but other studies observed that children who developed B-ALL aged 2–5 years had significantly more clinically diagnosed infectious illness episodes in the first year of life compared to controls [103]. This suggests that immune deregulation in children who develop ALL may be detectable several years before diagnosis [104, 105]. Further support for this observation is provided by demonstrating that Interleukin 10 levels in neonates are reduced in new-borns who develop leukaemia [106].

The influence of infections on HSC proliferation has been shown [107], thus confirming a relation with infections, immune system and inflammation on a molecular basis. Further studies should try to include the development and status of the immune system in the foetus compared to infants, young children and adults.

If a specific infectious agent is responsible for childhood leukaemia then it should be detectable. Identification of gene variants should be possible by revisiting already available single-nucleotide polymorphism (SNP) data. Deep sequencing should help finding the presence of pertinent viruses or epigenetic marks of their action if there was a virus-based hit-and-run mechanism, but it should be borne in mind that if childhood leukaemia is a rare response to a common infection then the responsible agent is likely to have infected most children, and only those in remote rural areas may have escaped infection.

3.6. *Animal models*

As an animal model, a ‘multi-hit’ model is highly desirable to study the mechanisms of initiating events (genetic, epigenetic or environmental hits) as well as the nature and role of the further hits, their kinetics and age-dependence and potential risk factors (intrinsic versus extrinsic factors: chemicals, radiation, infections/inflammation, immune control of malignant progression). For many years the existing animal models were only of limited versatility, and therefore the generation of new, more adequate animal models for childhood leukaemia is necessary [108, 109]. Mouse models can contribute in supporting hypotheses derived from human molecular studies, and vice versa, as for instance the contribution of gene variants or the identification of new (epi)genetic susceptibility genes.

The ultimate goal is to be able to mimic in the mouse the features of human B-cell ALL, at each level (molecule, cell, tissue, whole organism), including initiation, progression, evolution, response to therapy and eventual cure or relapse. Mouse models of B-cell ALL are useful for exploring the abnormal processes in haematopoiesis leading to leukaemia and the role of the immune system and for identifying fingerprints of exposure [77]. Other models, like the NOD/SCID mice, offer the possibility of studying premalignant human cord HSCs and follow up their development.

Additionally, the analysis of host genetic background in leukaemia development would give further benefits. In a well-defined mouse model the animals should be exposed to possible risk factors (radiation, chemicals, infections/inflammation, replicative stress, etc) followed by complete phenotyping with standardised protocols. A mouse model of controlled genetic

variability with a backcross between two syngeneic mouse strains (a resistant one and a susceptible one) would allow the assessment of the role of the various low-susceptibility genes.

4. Conclusions and recommendations

The Workshop participants suggested a general need for a better understanding of the causes of childhood leukaemia. This should also shed light in understanding childhood leukaemia near nuclear installations. The path forward should involve extended multidisciplinary collaborations to improve consistency of approaches between countries and researchers in order to facilitate a better understanding of the results regarding the occurrence of childhood leukaemia near nuclear installations. Overall, stronger networking amongst investigators in different disciplines involved in research on childhood leukaemia is warranted. This should be done in parallel with work that focuses on as accurate as possible exposure characterisation, limiting confounding, measuring differential bias, and controlling selection bias. To improve the understanding of the existing results, further work should focus primarily on childhood leukaemia, though noting that studies of other diseases may help interpretation (i.e. is the association confined to childhood leukaemia or not?).

It was emphasised that risk factors under consideration should be analysed in relation to childhood leukaemia subtypes, e.g. include tumour characterisation by genetic/epigenetic profiles in conjunction with epidemiological data. To that extent, the re-evaluation of existing material (e.g. from GWAS) in view of new hypotheses was seen as a promising way forward.

Focusing alone on the relationship between childhood leukaemia and nuclear installations is unlikely to help. Emphasis should be placed on better understanding of the causes of childhood leukaemia and how these causes are distributed among the childhood population. Ways forward have been pointed out, trying to integrate hypotheses and modern biological and experimental techniques, if possible. Research strategies need to take full account of the existing body of evidence, so that duplication of research is avoided and the focus is upon promising avenues of investigation.

The following recommendations can be highlighted from the MELODI Workshop:

- (a) The surveillance of childhood leukaemia incidence should be continued, not only around nuclear installations.
- (b) No specific epidemiological study design is recommended. Various approaches are potentially fruitful as long as they are based on prior hypotheses, provide accurate exposure estimates and avoid major biases.
- (c) Setting up of new studies on childhood leukaemia near nuclear installations is not necessary unless they include new features, e.g. a close link to research into the pathogenesis of childhood leukaemia. Collection of bio-specimens (e.g. cord blood or neo-natal blood spots) is important to allow research of biomarkers, and their analysis should be done at appropriate time windows.
- (d) Efforts should be made to harmonise exposure estimates (probably including the assessment of relevant incorporated radionuclides), to better characterise the population with respect to demography, urban/rural status, life habits and sociologic factors, patterns of population mixing, as well as other potential environmental risk factors including ELF-EMF, proximity of chemical factories, petrol stations, highways, etc.
- (e) Studies should distinguish between leukaemia subtypes, ensuring consistency of subgroup definitions across studies for comparability. Epigenetic/genetic profiles of childhood leukaemia should be used in conjunction with epidemiologic data.

- (f) The implementation of an international working group is recommended to better understand the variability of results between countries. This group would be a step forward to verifying the feasibility and pertinence of international pooling analysis. Specific aims of a pooled analysis are increasing statistical power to allow analyses of leukaemia subtypes, overcoming the problems of boundaries and harmonising the study designs.
- (g) Prevalence of the preleukaemic clone (ETV6-RUNX1 and other translocations) has to be determined.
- (h) Determining the relationship between leukaemia and the immune function is of major importance, especially regarding the hypothesis of an infectious cause. An urban–rural stratification of existing SNP array data should be done. Deep sequencing of the genomes of leukaemia cases should be extended to allow detecting potential viral sequences.
- (i) The linkage between epidemiology and experimental science needs to be improved. Animal studies can improve our understanding of the male:female ratio and the effects of birth weight, susceptibility targets, the role of immune system, and normal haematopoiesis and early stages of leukaemia development.

Activities have to be coordinated on a multi-national level. The European platform on low-dose research MELODI should assist in bringing scientists from different disciplines closer together, in interaction with international research consortia that already exist.

Appendix. List of participants (organisation, country)

Auvinen A (STUK, FI), Badie C (HPA, UK), Bithell J (CCRG, UK), Borkhardt A (U Duesseldorf, DE), Clavel J (INSERM, FR), Chartier M (IRSN, FR), Chokkalingam A (U Berkeley, USA), Cobaleda Hernandez C (CBMSO, ES), Dehos A (BfS, DE), Dekkers F (RIVM, NL), Dwyer T (MCRI, AUS), Empereur-Bissonnet P (InVS, FR), Grosche B (BfS, DE), Hémon D (INSERM, FR), Hornhardt S (BfS, DE), Infante-Rivard C (U McGill, CA), Jacob S (IRSN, FR), Jouve A (EC, BE), Kaatsch P (GCCR, DE), Kinlen L (Uni Oxford, UK), Kostı O (NAS, US), Kuehni C (U Bern, CH), Laurier D (IRSN, FR), Little M (NCI, US), Lightfoot T (Uni York, UK), Ohkubo C (EMF Inf Center, JP), Passegue E (UCSF, US), Repussard J (IRSN, FR), Richardson D (U N Carolina, US), Romeo Paul-H (CEA, FR), Rööslı M (U Basel, CH), Sanchez-Garcia I (IBMCC Salamanca, ES), Spycher B (U Bern, CH), Stanulla M (U Kiel, DE), Tirmarche M (IRSN, FR), Van Nieuwenhuysen A (WIV-ISP, BE), Voisin P (IRSN, FR), Wakeford R (U Manchester, UK), Weiss W (BfS, DE), Wojczik A (U Stockholm, SE), Zeeb H (BIPS, DE), Ziegelberger G (BfS, DE).

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